Newly Identified Safety Signal (NISS) Integrated Review Memorandum

Division of Non-Prescription Drugs 1 (DNPD1)
CDER Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

Drug name	Acetaminophen
SSID #	1001355
TSI open (create) date	May 15, 2014
Safety Issue Name	Maternal exposure during pregnancy
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Date	May 1, 2020

I. BACKGROUND

Tracked Safety Issue (TSI) 1355 for acetaminophen (APAP) and maternal exposure during pregnancy (i.e., neurodevelopmental effects, such as attention deficit/hyperactivity disorder, ADHD) was opened May 15, 2014. Two Division of Epidemiology 1 (DEPI) reviews (RCM # 2014-689 and RCM # 2015-387) and a Division of Nonprescription Drugs (DNDP) nonclinical review (dated February 8, 2016) were completed. Although data did not support a causal association, *Prescription and Over-the-Counter (OTC) Pain Medicines: Drug Safety Communication – FDA Review of Possible Risks of Pain Medicine Use during Pregnancy* was released on January 9, 2015 to inform the public of this issue. See Integrated Review (dated March 2, 2016), which recommended closing the TSI and resuming normal surveillance at that time.

Per 21 CFR 201.63, all APAP Drug Facts labels state, "**If pregnant or breast-feeding,** ask a health professional before use."

The following additional consumer information has been released by the Agency regarding the safe use of medicine during pregnancy:

- Consumer Update: Pregnancy: A Time for Special Caution (May 10, 2013)
- Medicine and Pregnancy (last updated May 19, 2017)[1]

In August 2016, Stergiakouli et al. published "Association of acetaminophen use during pregnancy with behavioral problems in childhood: Evidence against confounding" in the *JAMA Pediatrics*.[2] DNDP requested DEPI review this publication.

II. SIGNIFICANT REVIEW FINDINGS

[1] https://www.fda.gov/forconsumers/byaudience/forwomen/ucm118567.htm

[2] Stergiakouli E, Thapar A, Davey Smith G. Association of acetaminophen use during pregnancy with behavioral problems in childhood: Evidence against confounding. JAMA Pediatr. 2016 Aug 15. [Epub ahead of print]

On October 14, 2016, DEPI completed its review of neurodevelopmental outcomes following prenatal acetaminophen exposure (RCM # 2016-1871). In addition to the Stergiakouli article, it reviewed three additional studies.[3,4,5] The review concluded that eight observational studies have examined neurodevelopmental outcomes following prenatal APAP exposure. While the quality of the evidence varied across studies, seven showed some association with adverse neurodevelopmental outcomes (e.g., cognitive development, attention problems, motor development, autistic behaviors, and general behavioral problems). The review acknowledged the absence of proof of a causal relationship yet recommended seeking nonclinical input and a communication.

On February 10 and April 7, 2017, Division of Bone, Reproductive, and Urologic Products (DBRUP) and Division of Pediatric and Maternal Health (DPMH) completed their respective consults.

On January 24, 2018, the multidisciplinary Safety Issue Team (SIT) took this issue to the Medical Policy and Program Review Council (MPPRC). (See briefing materials and meeting minutes for full details.) MPPRC did not suggest making any labeling changes. It agreed that given the uncertainty as to whether there is a causal association, issuing a communication at that time would not add substantively to the prior DSC. Generally, most Council members did not support additional nonclinical studies if it was concluded that endpoint would be inadequate. However, it was recommended that the team reach out to the National Center for Toxicological Research (NCTR) to discuss potential studies that might address this issue, and the team come return to MPPPRC with a proposal that could shed light on this important issue.

On January 7, 2019, DEPI completed an analysis of urogenital outcomes with in utero acetaminophen exposure.

III. DISCUSSION

Medical Policy and Program Review Council Meeting Minutes (MPPRC)

See October 3, 2018 briefing materials and meeting minutes for full details.

The review team consulted the National Center for Toxicological Research (NCTR). NCTR's preliminary hypothesis is that the adverse neurodevelopmental effects, if present, could be the result of constriction of the ductus arteriosus (thereby altering fetal blood flow and potentially impacting neuronal development), the result of the known hepatotoxic effect of the drug given the small safety margin in animal toxicology studies, or the result of another peripheral mechanism. There are challenges when relying on an

[3] Avella-Garcia CB, Julvez J, Fortuny J, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. Int J Epidemiol. 2016 Jun 28. [Epub ahead of print]
[4] Liew Z, Ritz B, Virk J, Arah OA, Olsen J. Prenatal Use of Acetaminophen and Child IQ: a Danish Cohort Study. Epidemiology. 2016 Jul 28. [Epub ahead of print]
[5] Vlenterie R, Wood ME, Brandlistuen RE, Roeleveld N, van Gelder MM, Nordeng H. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero: a propensity score matched cohort study. Int J Epidemiol. 2016 Aug 31. [Epub ahead of print]

animal study to understand the link between ductus arteriosus constriction and neurodevelopmental affects because the peak period of brain development does not occur at the same time across all species.

(b) (5)

. The council discussed (b) (5) *—feeling that additional discussions on this would be in order.*

(b) (5)

The Council asked (b) (5) *. The Council was concerned that* (b) (5) .

However, the Council (b) (5) .

The Council recommended [redacted] (b) (5) .

European Medicines Agency (EMA)

On November 19, 2018, EMA updated the Agency on its review of paracetamol use in pregnancy and child neurodevelopment (EPITT No. 17796). EMA requested paracetamol sponsors revise the Summary of Product Characteristics (SPC) to state that epidemiologic studies have yielded conflicting results.

IV. RECOMMENDED REGULATORY ACTION

- As advised by MPPRC on October 3, 2018, continue to work with NCTR to [redacted] (b) (5) to evaluate this indeterminate risk
- Close the SSID in the Lifecycle Signal Tracker (LiST) and actively monitor
- Consider reopening the SSID when the study is complete

U.S. FOOD & DRUG ADMINISTRATION

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Date: 5/7/2020 4:18 PM EDT
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